REMARKS

Claims 7, 20, 21, 28-58 are pending in the application. Claims 34 and 35 have been amended, the amendment is supported in the specification at least at pages 5-6, as originally filed. Claim 39 has been amended to correct a spelling error.

New claims 40-58 have been added. None of the new claims incorporates new matter. Support for each of the new claims is found in the specification at least at page 4, lines 11-14, and page 6, lines 23-27.

I. Rejection Under 35 U.S.C. § 102(b) Based Upon Carr.

The Examiner has rejected claims 20 and 34 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,254,129 of Carr *et al.* ("Carr").

According to the Examiner's reasoning, Carr discloses a composition comprising 0.01 to 20 mg/kg of body weight of a patient of a piperidine derivative of formula (I) which includes fexofenadine when R_1 is -OH, R_2 is H, R_3 is -COOH, and n is 3. Additionally, the Examiner states that Carr discloses a carrier that can be propylene glycol or polyethylene glycol. The Carr composition is administered to warm blooded animals such as humans, cats, dogs, cows, lambs, mice, and guinea pigs.

The applicants respectfully traverse the rejection and request that it not be applied to new claims 40-58.

Carr describes a substituted piperidine derivatives including, when the R groups have certain substituents, fexofenadine. However, there is no disclosure in Carr of use of a pharmaceutical excipient that increases the solubility of fexofenadine or its salt in water that is a cyclodextrin or glycofurol. In addition, Carr does not disclose or suggest aqueous compositions comprising the additional element of an aqueous vehicle such as water and propylene glycol (or cyclodextrin or glycofurol) as is present in, *e.g.*, new claim 40.

Accordingly as Carr does not teach or suggest each element of the invention, it does not anticipate the claims. It is requested that the Examiner reconsider and withdraw this 35 U.S.C. § 102(b) rejection based upon Carr.

II. Rejection Under 35 U.S.C. § 102(e) or in the Alternative, 35 U.S.C. § 103(a) as Obvious Over U.S. Patent No. 6,103,735.

The Examiner has rejected claims 30-33, 35, and 37 under 35 U.S.C. § 102(e) as anticipated by, or, in the alternative, under 35 U.S.C. § 103(a) as obvious over, U.S. Patent No. 6,103,735 of Aslanian *et al.* ("Aslanian") The Examiner contends that Aslanian discloses a composition and method of using the composition to treat allergic rhinitis, asthma, and related disorders. The Aslanian composition, as characterized by the Examiner, includes a therapeutically effective amount of at least one neurokinin agonist, a therapeutically effective amount of at least one H_3 antagonist, and a therapeutically effective amount of at least one H_1 antagonist. The Examiner contends that fexofenadine is an example of an H_1 receptor agonist. The Aslanian composition further comprises carriers, binders, lubricants, disintegrants, such as, starch, gelatin, sodium alginate, polyethylene glycol, carboxymethyl cellulose, sodium benzoate, sodium chloride, guar gum, sweetening, and flavoring agents. The Examiner asserts that Aslanian teaches that liquid formulations of the composition contain propylene glycol in a water-propylene glycol solution.

The applicants respectfully traverse this rejection and request that it not be applied to the new claims.

First, Aslanian does not anticipate the invention for it does not teach each element of the invention. Specifically, Aslanian describes pharmaceutical compositions that are useful in the treatment of allergic rhinitis and include a combination of therapeutically effective amounts of one or more neurokinin antagonists, H_3 antagonists, and/or H_1 antagonists, of which fexofenadine is disclosed as an example. Liquid preparations of the Aslanian composition may contain propylene glycol. However, Aslanian discloses no other components for use in aqueous solutions or liquid preparations of the Aslanian composition.

In contrast, the claims of the invention include a composition that consists essentially of fexofenadine and a pharmaceutical excipient that increases the solubility of the fexofenadine or its salt in water that is a cyclodextrin or glycofurol. Neither of these pharmaceutical excipients are disclosed in Aslanian for use in increasing the solubility of fexofenadine or its salt in an aqueous solution. In addition, none of the compositions of Aslanian disclose an additional aqueous vehicle. Thus, Aslanian does not disclose each element of the invention and does not anticipate it.

Moreover, Aslanian does not render obvious the claimed invention. First, for at least the reasons discussed above, Aslanian does not teach or suggest each element of the invention as claimed. A person of ordinary skill in the art would have had no motivation to modify the teachings of Aslanian to arrive at the present invention. Aslanian provides no teaching of the significance of increasing the solubility of fexofenadine in an aqueous solution that would have caused a person of ordinary skill to substitute the polyethylene glycol for other pharmaceutical excipients that increase the solubility of the fexofenadine.

Although it is stated in Aslanian that the H_1 antagonist may be present in an amount of 1 to 200 mg, there is no suggestion that a concentration of 100 μm/ml to 100 mg/ml could be a suitable concentration of fexofenadine to use, or that this concentration is particularly suitable for compositions for delivery of fexofenadine to the eye or nose. In addition, although water-propylene glycol solutions are discussed in Aslanian, they are referenced as suitable for solutions for use in parenterel injections and oral solutions. A person of ordinary skill in the art reading Aslanian would have known that the fexofenadine has a low solubility in water. There is nothing in Aslanian that would have suggested to him that the use of a combination of water and propylene glycol could provide a solution containing a sufficient amount of solubilized fexofenadine to make it suitable for delivery to the eye or nose.

Therefore, for at least these reasons it is submitted that the disclosure of Aslanian neither anticipates nor renders obvious the invention as claimed. Reconsideration and withdrawal of the rejection is respectfully requested.

III. Rejection Under 35 U.S.C. § 102(e)/§ 103(a) Based Upon U.S. Patent No. 6,451,815.

The Examiner has rejected claims 30-33, 35 and 37 under 35 U.S.C. § 102(e) as anticipated by, or, in the alternative, under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 6,451,815 of Hwang *et al.* ("Hwang"). As basis for the rejection, the Examiner contends that Hwang discloses a composition comprising an antihistamine of a specific structure or its pharmaceutically acceptable salt, and that such structure encompasses fexofenadine when R is a hydrogen atom. The Examiner states that Hwang discloses a combination of fexofenadine and p-glycoprotein inhibitors such as poloxamer, polyethylene glycol, polyethylene castor, and vitamin E, and additional adjuvants or excipients. The Examiner concedes that the Hwang formulation is not taught as having a specific concentration of fexofenadine, but discloses only that the formulation contains 1 mg to 500 mg of fexofenadine as a daily dose. The Examiner contends

that either at a certain dosage the concentration would be the same and/or if not, it is within the purview of a person of ordinary skill in the art to modify the concentration to arrive at of the invention as claimed.

The applicants respectfully traverse the rejection and request that it not be applied to the new claims.

Hwang discloses compounds of a specific formula such that when R is a hydrogen atom, the formula is that of fexofenadine. Hwang discloses compositions containing the compound of formula (I) and a p-glycoprotein inhibitor in the form of a solution or suspension that may contain adjuvants such as propylene glycol. Further, no other pharmaceutical excipients that increase the solubility of fexofenadine in water are taught. Moreover, there is no disclosure in Hwang of an aqueous composition containing fexofenadine and propylene glycol. In the examples, the compositions that include fexofenadine and propylene glycol are in the form of a solid tablet for oral administration and are therefore, by definition, not solutions of any kind, let alone aqueous compositions. Thus, as Hwang does not disclose each element of the invention a claimed, it does not anticipate it.

Moreover, Hwang does not render the claimed invention obvious. First, for the reasons discussed above, the disclosure of Hwang is missing at least one element of the invention as claimed. No teaching or suggestion of the missing element is provided in Hwang. A person of ordinary skill in the art would not have been motivated to modify the teachings of Hwang to arrive at the invention as claimed. There is no discussion in Hwang of the necessity or the desirability of increasing the solubility of fexofenadine in water. Indeed, the exemplary compositions provided in Hwang are not liquid compositions at all, but are solid compositions, *i.e.,* tablet or capsule. Thus, there would have been no motivation provided for a person of ordinary skill in the art to modify Hwang by seeking pharmaceutical excipients that increase the solubility of fexofenadine in water, such as cyclodextrin and glycofurol. Additionally, there is no disclosure in Hwang that would have encouraged a person of ordinary skill in the art to provide an aqueous solution comprising fexofenadine and propylene glycol. All of the compositions including fexofenadine with propylene glycol specifically disclosed in Hwang are solid compositions. Thus, the solubility of fexofenadine in water was not an issue. Moreover, because this issue of solubility was not addressed, there is no evidence in Hwang that the aqueous compositions containing the amount of fexofenadine specified in claims 35 and 41 of

the application could actually be achieved. The dosage forms referenced by the Examiner are, again, not aqueous, but are in fact, solid.

Finally, because the compositions of Hwang are intended to provide systemic release of the compounds of formula (I) through oral administration, and the compositions of the invention are intended to provide local release of fexofenadine to the eye or nose, a person of skill would not attempt to modify the solid dosage forms of Hwang by developing liquid solutions, and then take the additional modification step of increasing the solubility of fexofenadine in water.

Accordingly, for at least these reasons, it is respectfully submitted that the Examiner's rejection under 35 U.S.C. § 102(e)/35 U.S.C. § 103(a) is overcome as the claims are neither anticipated nor rendered obvious by Hwang. It is requested that the Examiner reconsider and withdraw the rejection.

IV. Rejection Under 35 U.S.C. § 103(a) Based Upon Carr -- Claim 21.

The Examiner has rejected claim 21 under d35 U.S.C. § 103(a) as being unpatentable over Carr taken in view of Hwang. As basis for the reasoning the Examiner states that Carr discloses administration of a composition comprising fexofenadine to a subject by intranasal instillation or topical application to mucus membranes of the nose, throat, or bronchial tubes. Carr, concedes the Examiner, is silent on the treatment of rhinitis. The Examiner remedies this deficiency by applying the disclosure of Hwang, which is relied upon for a teaching of rhinitis with fexofenadine.

The applicants respectfully traverse the rejection and request that it not be applied to the new claims.

First, for the reasons discussed above, neither Carr nor Hwang teach or suggest each element of the invention as claimed. In particular, both references are silent on the use of pharmaceutical excipients that increase the solubility of fexofenadine or its salt in water that are cyclodextrin and glycofurol, nor does each discuss the use of an aqueous composition containing fexofenadine and propylene glycol and an additional aqueous vehicle.

In addition, a person of skill in the art would not have been motivated to combine the teaching of Hwang with the specific teaching of Carr. In Hwang it is taught that the composition is specifically designed for systemic administration of the selected active compound. In contrast, Carr discusses administration by application to mucosal membranes. A person of skill in the art

would not combine two references disclosing two very distinct routes of administration in order to arrive at the invention as claimed.

Accordingly, it is submitted that the combination of Carr and Hwang as proposed by the Examiner does not render obvious the invention. Reconsideration and withdrawal of the rejection is respectfully requested.

V. Rejection Under 35 U.S.C. § 103(a) Based Upon Carr-Hwang -- Claims 28, 29, 38, 39.

The Examiner has rejected claims 28, 29, 38, and 39 under 35 U.S.C. § 103(a) as being unpatentable over Carr taken in view of Hwang. The Examiner contends that Carr teaches the claimed fexofenadine composition with the exception that a gelling agent that is a bioadhesive is not taught. To remedy this deficiency the Examiner applies Hwang. Hwang teaches a fexofenadine formulation that contains a gelling agent of a bioadhesive, such as a poloxamer or starch polysaccharide. The Examiner argues that one of ordinary skill would have been motivated to include the poloxamer of Hwang with the expectation of enhancing the bioavailabilty of fexofenadine.

The applicants respectfully traverse the rejection and request that it not be applied to the new claims.

First, for the reasons discussed above, neither Carr nor Hwang teach or suggest all elements of the claimed composition. There is nothing in Hwang that would have encouraged a person of ordinary skill in the art to use a gelling agent or a bioadhesive material. Hwang does not discuss or address this issue nor does it teach use of a pectin, alginate, gellan, or chitosan. Starch, is used in Hwang as a binder, not to increase bioavailability or to use as a gelling agent. Poloxamers are described in Hwang as being among p-glycoprotein inhibitors. There is no suggestion that they could be used as gelling agents to provide controlled release of fexofenadine within the nasal cavity or eye.

In view of the foregoing, it is submitted that the rejection of the claims based upon the combination of Hwang and Carr is overcome. Reconsideration and withdrawal of the rejection is requested.

VI. Rejection Under 35 U.S.C. § 103(a) Based Upon Chen -- Claims 35 and 36.

The Examiner has rejected claims 35 and 36 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,267,985 of Chen *et al.* ("Chen"). The applicants

respectfully traverse this rejection, as Chen is not properly cited as prior art against the claims of this application.

The earliest prior art date for Chen is its filing date, June 30, 1999. This application claims priority to, and is therefore entitled to the benefit of, United Kingdom application 9822170.8, filed October 13, 1998. The priority date of this application in 1998 is before the earliest prior art date of the Chen patent. Therefore, Chen cannot be properly cited against this application as prior art under any subpart of 35 U.S.C. § 102 or § 103.

Accordingly, it is requested that the Examiner reconsider and withdraw the rejections based upon Chen.

VII. Claim 25

The Examiner suggested that claim 25 be amended to recite the amount of fexofenadine in different units than are already present in the claim. The applicants respectfully submit that the units presently recited in the claim are well within the understanding of a person of ordinary skill in the art and, in fact, are the usual notation for such concentrations. The fact that the units are not identical does not detract in any way from their clarity or definiteness. Accordingly, the applicants prefer that claim 25 remain in its present state.

CONCLUSION

In view of the foregoing, it is submitted that pending claims 7, 20, 21, 28-58 are patentable over the cited references. Thus, reconsideration and allowance of the claims at the earliest opportunity is respectfully requested.

Respectfully submitted,

Lisbeth Illum, *et al.*

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